Radiopharmaceutical and Gene Therapy Program
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Most recent report of results to date:

1. **Introduction.** The objective of our research program was to determine whether novel receptors can be induced in solid cancers as a target for therapy with radiolabeled unmodified peptides that bind to the receptors. The hypothesis was that induction of a high number of receptors on the surface of these cancer cells would result in an increased uptake of the radiolabeled monomeric peptides as compared to published results with radiolabeled antibodies or peptides to naturally expressed antigens or receptors, and therefore a better therapeutic outcome. The following is a summary of published results.

2. **Induction of receptors *in vivo*.** To evaluate the ability to induce receptor expression *in vivo*, a replication-incompetent adenovirus (Ad) encoding the gene for hSSTr2 under control of the cytomegalovirus promoter (AdCMVhSSTr2) was injected *i.p.* to induce hSSTr2 expression on SK-OV-3.ip1 tumors growing in the peritoneum in nude mice. Tumor localization of ^{111}In-DTPA-D-Phe1-octreotide 4 h after i.p. injection was equal to 60.4% ID/g of the radiolabeled peptide. Other studies investigated the localization of ^{111}In-DTPA-D-Phe1-octreotide to *s.c.* A-427 non-small cell lung tumors injected intratumorally (*i.t.*) with AdCMVhSSTr2. The region of interest (ROI) analysis after gamma camera imaging showed the tumor uptake of ^{111}In-DTPA-D-Phe(1)-octreotide to be 2.8% ID/g 48 h after injection and 3.1% ID/g at 96 h. Gamma camera imaging was used to detect hSSTr2 expression in *s.c.* A-427 tumors infected with AdCMVhSSTr2 using a ^{99m}Tc- or ^{188}Re-labeled somatostatin analogue P829. Independent confirmation of hSSTr2 expression was demonstrated by immunohistochemical analysis.

   A novel ^{99m}Tc-labeled peptide (P2045) binds with high affinity to hSSTr2 and has favorable *in vivo* biodistribution. We evaluated this peptide in mice bearing SK-OV-3.ip1 tumors in the peritoneum. Tumor uptake of ^{99m}Tc-P2045 at 48 h after *i.v.* injection averaged 2.2 ± 0.3% ID/g for mice injected *i.p.* with AdCMVhSSTr2 ($1x10^9$ pfu). We also evaluated ^{99m}Tc-P2045 in mice bearing *s.c.* A-427 tumors injected *i.t.* with AdCMVhSSTr2 or with a control Ad. The images showed radioactive uptake in the tumors injected with AdCMVhSSTr2 but background uptake in tumors injected with control Ad.

   Further studies have been reported using a bicistronic Ad vector encoding hSSTr2 and thymidine kinase (TK) in the same mouse tumor model. The A-427 tumors were injected *i.t.* with the bicistronic vector (AdCMVhSSTr2TK) and the animals imaged for hSSTr2 expression with ^{99m}Tc-P2045 and TK with ^{131}I-FIAU. The biodistribution results showed the uptake of ^{99m}Tc-labeled P2045 and ^{131}I-labeled FIAU for AdCMVhSSTr2TK-injected tumors was 11.1% and 1.6% ID/g, respectively.

   A separate therapy study was conducted with nude mice bearing naturally SSTR-positive AR42J rat pancreatic tumors. High tumor retention of ^{188}Re-P2045 was observed. Results of a therapy study with 4 treatments over 2 weeks were previously presented. There was a clear relationship between tumor response and dose of ^{188}Re-P2045.

3. **Therapy studies with the single gene vector AdCMVhSSTr2 and ^{90}Y-SMT 487.** Another somatostatin analogue that has been used for therapy is ^{90}Y-DOTA-D- Phe(1)-Tyr^{3}-octreotide (^{90}Y-SMT 487). Nude mice were inoculated *s.c.* with A-427 cells. Twenty-four days later the mice were administered 1 x 10^{9} pfu AdCMVhSSTr2 intratumorally (Day 0). Mice that received 2 *i.t.* injections of AdCMVhSSTr2 and 4 doses of 400 μCi or 500 μCi ^{90}Y-SMT 487 had median tumor quadrupling times of 40 and 44 days, respectively. The log-rank test revealed a statistically significant difference in time to tumor quadrupling between the AdCMVhSSTr2 + ^{90}Y-SMT 487 treatment groups and the control groups ($p<0.02$).

4. **Therapy studies with the bicistronic vector AdCMVhSSTr2CD and ^{90}Y-SMT 487.** We constructed and evaluated bicistronic Ad vectors encoding for hSSTr2 and the CD enzyme. The CD converts the non-toxic prodrug 5-FC to the cytotoxic and radiosensitizing drug 5-FU. We investigated imaging of gene transfer in athymic nude mice bearing *s.c.* A-427 tumors injected with 1x10^{9} pfu AdCMVhSSTr2 or AdCMVhSSTr2CDRGD. After 2 days, ^{99m}Tc-P2045 was *i.v.* injected and gamma camera imaging demonstrated localization in the tumors.

   Therapy studies were initiated with AdCMVhSSTr2CD and ^{90}Y-SMT 487 in combination with 5-FC. Tumor inhibition results showed that both ^{90}Y-SMT 487 and ^{90}Y-SMT 487 in combination with 5-FC slowed tumor growth. Importantly, the combination treatment produced a greater tumor growth inhibition than the ^{90}Y-SMT 487 treatment alone and the levels of toxicity (weight loss) were modest. However, as with the ^{90}Y-SMT 487 treatment alone, the tumors eventually regrew at an exponential rate. Therefore, further modification of this therapeutic regimen was necessary.

5. **Therapy with the bicistronic vector AdCMVhSSTr2CD, ^{90}Y-SMT 487, and external beam radiation.** The rationale behind the use of ^{60}Co with our therapeutic approach is that external beam radiation is used in the treatment of many cancers and it can simulate the higher radiation dose delivered to tumor when a better radiolabeled peptide is used. Tumor inhibition results were extremely encouraging as they show that the combination of ^{90}Y-SMT 487 + 5-FC + 3 Gy resulted in tumor regressions. All combination therapies had at least two complete regressions with most being recurrence-free. The triple therapy groups had the greatest mean tumor growth suppression over all treatment groups.

Most recent products delivered:

1. Rogers BE, McLean SF, Kirkman RL, Della Manna D, Bright SJ, Olsen CC, Myracle AD, Mayo MS, Curiel DT, Buchsbaum DJ: *In vivo* localization of [^{111}In]-DTPA-D-Phe1-octreotide to human ovarian tumor xenografts induced to express the somatostatin receptor subtype 2 using an adenoviral vector. *Clin Cancer Res* 5:383-393, 1999.

2. Buchsbaum DJ: Imaging and therapy of tumors induced to express somatostatin receptor by gene transfer using radiolabeled peptides and single chain antibody constructs. *Semin Nucl Med* 34:32-46, 2004.

3. Buchsbaum DJ, Chaudhuri TR, Zinn KR: Radiotargeted gene therapy. *J Nucl Med* 46:179S-186S, 2005.

4. Zinn KR, Chaudhuri TR, Krasnykh VN, Buchsbaum DJ, Mountz JM, Belousova N, Grizzle WE, Curiel DT, Rogers BE: Gamma camera dual imaging with a somatostatin receptor and thymidine kinase after gene transfer with a bicistronic adenovirus. *Radiology* 223:417-425, 2002.

5. Zinn KR, Buchsbaum DJ, Chaudhuri TR, Mountz JM, Grizzle WE, Rogers BE: Noninvasive monitoring of gene transfer using a reporter receptor imaged with a high-affinity peptide radiolabeled with ^{99m}Tc or ^{188}Re. *J Nucl Med* 41:887-895, 2000.

6. Rogers BE, Zinn KR, Lin C-Y, Chaudhuri TR, Buchsbaum DJ: Targeted radiotherapy with [^{90}Y]-SMT 487 in mice bearing human nonsmall cell lung tumor xenografts induced to express human somatostatin receptor subtype 2 with an adenoviral vector. *Cancer* 94:1298-1305, 2002.

Most recent notes concerning the project:

None

Other Project Information Sources:

Project URL:

None

Related URL at institution:

None